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VIA HAND DELIVERY

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: FDA "Draft Guidance For Industry on ANDAs: Blend Uniformity Analysis" [Docket No. 99D-2635]

Dear Sir/Madam:

Barr Laboratories, Inc. ("Barr") requests that the Food and Drug Administration ("FDA") rescind the "Draft Guidance for Industry on ANDAs: "Blend Uniformity Analysis ("BUA")" [hereinafter the "Draft Guidance"], as well as stay the implementation of the agency's BUA ANDA approval requirement. For reasons discussed below, BUA testing as an in-process control is scientifically unnecessary and unjustifiable, as well as legally unenforceable.

SUMMARY OF BARR'S OPPOSITION

By issuing the Draft Guidance, FDA implies that BUA testing is a reproducible and relevant routine in-process control. Barr strongly disagrees with this position[1]. To date, the pharmaceutical industry as a whole has not embraced BUA testing as a scientifically valid in-process batch control. The critical question therefore is why is FDA proposing to replace a well established, accepted industry process/product BUA validation practice with batch release testing criteria that has yet to be scientifically accepted and validated.

Equally important is the fact that FDA has no legal basis for requiring regular BUA in-process testing. Admittedly, FDA regulations require the validation of manufacturing processes such as product mixing, as well as the submission, where appropriate, of information on in-

[1] As recently as last month, the generic industry voiced their rejection of in-process BUA testing at an industry/FDA meeting, while the Pharmaceutical Research and Manufacturers Association ("PhRMA") voiced their opposition to the Draft Guidance in written comments, dated Oct. 26, 1999.

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process controls used to ensure the quality and consistency of the final product. 21 C.F.R. §§ 210.110, 314.50 & 314.94. Yet, nowhere in the regulations is it specified that routine in-process BUA testing is required for such regulatory compliance. Although FDA asserts that the Draft Guidance is merely a "recommendation" for manufacturers seeking to comply with the regulations, the agency's actions and conduct indicate otherwise. Specifically, Barr contends that the implementation of the Draft Guidance, coupled with the agency's BUA ANDA approval policy requires certain ANDA applicants to: (1) commit to BUA testing as a condition of approval, and (2) retain such testing requirements post approval either as an ANDA or cGMP requirement. The net effect of these actions, and the agency's ultimate objective is the creation of a new industry, in-process release control. The agency, however, has failed to comply with notice and comment rulemaking procedures as required by the Act and Administrative Procedure Act.

Finally, Barr objects to the FDA's intent to impose these new obligations on ANDA applicants, without promulgating similar requirements for manufacturers of NDA products. In the event that BUA testing is determined to be a justifiable and valid in-process control that is required to ensure the quality and consistency of finished drug products, there is no scientific, public health, or other justification for limiting the application of such requirement to ANDA products.

For these reasons, which are discussed in more detail below, Barr requests that FDA withdraw the Guidance and end its informal policy of requiring in-process BUA for ANDA approvals.

DISCUSSION

A. The Draft Guidance Substitutes Arbitrary, Scientifically Unsupported Procedures for Well-Established and Scientifically Valid Industry Practices

Barr believes that the agency has failed to provide a sound scientific or public health justification for imposing this new obligation for manufacturers to conduct routine in-process BUA testing. On the scientific front, there are several outstanding issues regarding the applicability, validity and reproducibility of BUA testing as a regular, in-process control. Until these technical issues are resolved, FDA has no reliable scientific basis for requiring routine BUA testing as a condition precedent for ANDA approval or for cGMP compliance. Moreover, FDA lacks the necessary scientific justification for replacing the well-established, accepted industry cGMP process/product validation practice with the BUA testing criteria espoused in

both the Draft Guidance and ANDA deficiency letters.[2] As a result, the implementation of the Draft Guidance will impose substantial burdens on pharmaceutical manufacturers without creating any corresponding increase in product quality or related public health benefit.

With regard to the scientific validity of FDA's position, it is well-established that BUA testing, presents substantial variability stemming from the thief, methodology, and the product itself. In fact, the court in United States v. Barr Laboratories acknowledged the difficulties inherent in BUA testing. 812 F. Supp. at 458. Moreover, the agency readily admitted at a recent Industry/Agency meeting that the proposed acceptance criteria (90 to 110 percent of the expected quantity of active ingredient, with a relative standard deviation (RSD) of no more than 5%) is not grounded on scientific evidence. Rather, the agency based the conclusion on its experience with ANDA approvals, a suspect practice suggesting that the proposed rigid criteria are arbitrary, lacking a sound scientific rationale.

Not only does the Draft Guidance fly in the face of scientific reason, the lack of two-tier testing will lead to a substantial increase in the number of batches that must be rejected. This will result in an imposition of substantial burden, and cost on drug manufacturers. The imposition of such unwarranted new burdens on industry ignores the general thrust of the White House's "Reinventing The Government" initiative, which is designed to eliminate excessive and burdensome regulations that exhibit no countervailing justifications. See, e.g., Exec. Order 12866, 58 Fed. Reg. 513735 (Sept. 30, 1993); see also Exec. Order 12291, 46 Fed. Reg. 13193 (Feb. 17, 1981). Currently, industry practice allows manufacturers to reexamine problems encountered in testing. If manufacturers were required to discard commercial batches due to a one-tier system as required by the Guidance, or because of arbitrary parameters as set in the Guidance, the cost of manufacturing would likely increase needlessly for a vast majority of ANDA applicants.

Equally important, the Draft Guidance will cause manufacturers to abandon quality control practices that are valid and well-established. For instance, as previously noted, the Draft Guidance overrides the industry practice of using a two-tier testing system. Draft Guidance at 4. Such a disallowance of two-tier acceptance criteria is unjustified and allows for no variability due to sampling bias, even though variability is inherent to BUA due to currently available sampling techniques. The United States Pharmacopoeia applies a two-tier system for determining Uniformity of Dosage units (where scientifically sound analytical methods already

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[2] The Guidance instantly renders illegal existing Barr practices that have received favorable review from two FDA District Offices, the Department of Justice, and a federal court. Moreover, the Draft Guidance departs substantially from FDA's previous position on the matter. F-D-C Reports, Inc.; Pink Sheet 58(43):T&G 12-13 (Oct. 21, 1996).

exist). In fact, according to the United States Pharmacopoeia, a multi-tier system applies whenever measurements are taken from individual dosage units. Barr also refers FDA to the extensive discussion of two-tier testing in United States v. Barr Laboratories, in which Judge Wollin recognized the established nature and validity of two-tier testing for BUA. 812 F. Supp. at 469-70, 473.

Lastly, the Draft Guidance has been issued at a time when the Product Quality Research Institute is preparing to consider the myriad scientific issues surrounding BUA.[3] In public statements, agency officials have clearly stated that FDA is committed to working with PQRI to ensure that regulatory burdens imposed upon industry are scientifically justifiable. Yet, in contrast to such statements, the agency is moving forward with implementation of its new policy without utilizing the expertise of PQRI. Barr is aware that several organizations have called upon FDA to delay implementation until all scientific issues have been addressed through the PQRI or another public forum. Barr believes that the complex scientific issues, and the burdens imposed by the new policy, make such a delay appropriate. To consult with the PQRI *post hoc* defeats its purpose, which is to imbue agency's decision-making with sound science.

B. The Draft Guidance Establishes New Application Content and cGMP Requirements for ANDA Products, Which Require Compliance with the Administrative Procedures Act

FDA goes to great length to cast the Draft Guidance as merely agency "recommendations" for compliance with ANDA and cGMP regulations.[4] The agency first references regulations requiring the submission, as part of an original ANDA, of a description of in-process controls, specifications and other analytical methods used in the manufacture of the drug product. Draft Guidance at 1. The Draft Guidance also provides that FDA's cGMP regulations require the performance of a test on each commercial batch to monitor output and validate manufacturing processes that could cause variability. Draft Guidance at 3. The FDA concludes that routine in-process BUA testing satisfies both of these requirements with regard to homogeneity and uniformity. Draft Guidance at 1, 3.

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[3] PQRI is currently examining whether blend uniformity testing ensures end product quality. F-D-C Reports, Inc.: The Pink Sheet 61(47):28 (Nov. 22, 1999).

[4] This is understandable, given that FDA is not permitted to establish legally binding requirements through the guidance document process. See 21 C.F.R. § 10.90(b)(1); 62 Fed. Reg. 8961, 8967 (Feb. 27, 1997) (FDA's Good Guidance Practices).

While the above agency statements, taken alone, could be interpreted as setting forth agency recommendations, the agency's intent and conduct concerning routine in-process BUA testing indicates that it is anything, but voluntary. The mandatory import of routine BUA testing is illustrated by the implementation of the guidance as well as ANDA approval deficiency letters. For example, with respect to the Draft Guidance, the agency explicitly provides that ANDA applicants may request for the deletion of routine BUA testing post-approval only if such testing also is part of the applicant's cGMPs. If not, the applicant must provide supportive information justifying that BUA testing would not be necessary under cGMPs. Draft Guidance at 3. Yet, a review of such requests suggests that the agency does not exactly mean what it says. Specifically, FDA stated the following in an ANDA deficiency letter received recently by Barr Laboratories:

> We regret to inform you that the deletion of blend uniformity testing is not acceptable at this time. The Field District Office monitors blend uniformity analysis (BUA) on *all* post approval production batches. Please be aware that that OGD Policy regarding the in-process control BUA testing specification *recommends* that the acceptance criteria be established at 90-110% with an RSD of NMT 5.0%. *Please revise and resubmit your in-process control blend uniformity criteria to comply with the recommended specification.*

Letter from Florence S. Fang, FDA Office of Generic Drugs, to Barr Laboratories, Oct. 12, 1999 (ANDA 40-145/S-027) (emphasis added).

Given the agency's rigid application of routine BUA in-process testing, manufacturers have no option but to accept FDA's BUA "recommendations" in order to secure ANDA approvals as well as prevent cGMP non-compliance sanctions. As a result, FDA is creating a new, substantive binding requirement within the meaning of 5 U.S.C. § 553. Such a requirement should be subject to notice and comment rulemaking. See Syncor Int'l Corp. v. Shalala, 127 F.3d 90, 94 (D.C. Cir. 1997).

Courts have struck down similar attempts by FDA to establish binding requirements through the use of draft guidances. See Community Nutrition Institute v. Young, 818 F.2d 943 (D.C. Cir. 1987); United States v. Bioclinical Systems, Inc., 666 F. Supp. 82 (D. Md. 1987). In Bioclinical, FDA attempted to establish a GMP requirement through a draft guidance. In court, FDA conceded that the new requirement was not an industry standard, so it argued that the requirement constituted a GMP "independently of the draft guideline." Bioclinical, 666 F. Supp. at 83. In short, the agency contended that it can dictate what the GMPs are, even if the industry has not adopted them. The court disagreed, concluding that Congress provided for a rulemaking process, and it is through this process that FDA may set its particular requirement.

As in the Bioclinical case, FDA is attempting to use the cGMP and ANDA regulations as justification for the new routine in-process BUA requirement. Yet, FDA has interpreted its regulations far too broadly. As noted by a U.S. district court in an exhaustive discussion of cGMP requirements, section 211.110(a)(3) requires in-process controls only "where appropriate," and that "the mechanics of test taking [are] left undefined by the regulations." United States v. Barr Laboratories, Inc., 812 F. Supp. 458, 466, 475 (D.N.J. 1993). In that case, Judge Wollin correctly concluded that the FDA's cGMP regulation establishes broad requirements in an inherently flexible system, by which each firm may choose its own appropriately validated means to reach the intended goal – the production of a consistent, high quality finished drug product. He recognized that firms conduct in-process BUA during the product development phase to establish and validate blend times, and that BUA testing is a scientifically sound process validation tool. See 812 F. Supp. at 475. It cannot be inferred, however, from either Judge Wollin's opinion or the language of section 211.110, that routine BUA in-process testing is required by the cGMP regulation. In fact, one logically reaches the opposite conclusion—that once blend times are established and validated, BUA of every batch is no longer necessary, when other adequate means ensure product homogeneity and uniformity, such as content uniformity testing. To the extent that the Draft Guidance requires routine BUA in-process testing as part of cGMP, it exceeds the scope of the agency's own regulations.

C. FDA Has Provided No Adequate Justification for Applying the New Requirements to ANDA Products Only

Despite FDA's desire to apply the Guidance to all dosage forms and interpret the policy broadly, it remains unexplained why this new requirement fails to include NDA products. While footnote 3 of the Guidance indicates that FDA is waiting for an earlier draft guidance to be finalized before requiring BUA testing for NDAs, the agency fails to provide any rationale for why in-process BUA testing should apply to ANDAs now, and to NDAs later. Moreover, it is baffling why FDA has decided, for the time being, to interpret and implement cGMP requirements in 21 C.F.R. § 210.110(a)(3) in two different manners–one for NDAs, another for ANDAs. This disparate treatment vehemently argues against FDA's scientific justification for regular BUA testing.

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For the reasons stated, Barr Laboratories believes that FDA should withdraw the Draft Guidance and end its informal policy of requiring in-process BUA for ANDA approvals.

Sincerely,

Kathleen D. Jaeger

Kathleen D. Jaeger
On behalf of Barr Laboratories, Inc.

KDJ/drw/mpk